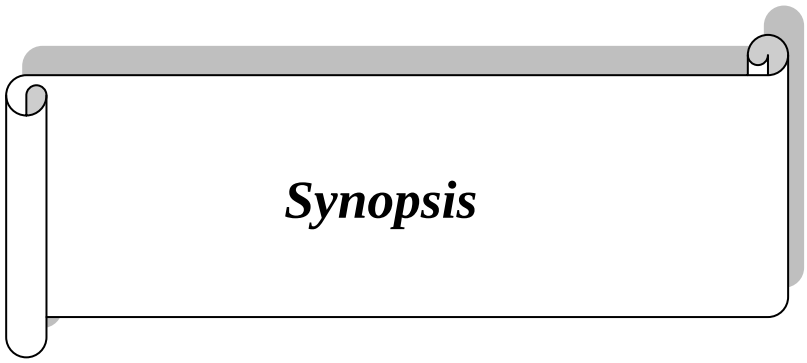

Synopsis

SYNOPSIS

The thesis entitled "**DEVELOPMENT OF ENYNE-ASSISTED ANNULATIONS TO SUBSTITUTED THIOPHENES, BENZOTHIOPHENES, INDOLES AND CARBAZOLES**" has been alienated into three chapters.

CHAPTER-I

SECTION A : This section describes "The introduction on enyne-assisted annulation reactions".

SECTION B : This section describes "A thioannulation approach to substituted thiophenes from MBH acetates of acetylenic aldehydes".

CHAPTER-II : Chapter **II** describes "A novel [4+2]-benzannulation of 3-alkenyl thiophenes/pyrroles with propargylic alcohols to access substituted benzothiophenes/indoles.

CHAPTER-III : Chapter **III** describes "One-pot sequential propargylation, cycloisomerization strategy to diversely substituted carbazoles and aryl or heteroaryl annulated[*a*]carbazoles.

CHAPTER-I

SECTION A: "Introduction to Enyne assisted annulation reactions"

The annulation reaction is a powerful atom economic method to access multisubstituted cyclic structures including both carbocycles and heterocycles from acyclic or cyclic precursors. Annulation reactions offer several advantages over classical linear substitution strategies, mainly in the preparation of highly substituted target molecules. These annulation routes frequently avoid the regiochemical ambiguities associated with aromatic substitution reactions and provide access to substitution patterns that cannot be obtained *via* the conventional routes. In the literature, there are different types of annulation reactions such as Diels-Alder reactions, acid-catalyzed polyolefin cyclizations, photo-chemical, radical and thermal cyclization reactions, which involves the unsaturated precursors like aldehydes, ketones, alkenes, alkynes, α, β-unsaturated compounds and enynes. Among these, enynes are suitable precursors for the construction of highly substituted target molecules and also offers simplifying strategies to complex molecules.

Organic molecules with combination of alkene (ene) and alkyne (yne) functionalities are known as enynes. These are important and versatile synthetic intermediates and discovered to be one of the most efficient starting materials to variety of cyclic structures, in addition to offering differentiated π-systems for selective functionalization. From the past few decades enynes are playing a significant role in annulation reaction, as it offers a facile access to wide range of useful heterocyclic and carbocyclic compounds.

Based on the position of ene and yne functions, enynes are usually addressed as 1,n enynes such as short tethered, 1,3 and 1,4-enynes and long-tethered, 1,5-, 1,6-, and 1,7-enynes. The behaviour of 1,n-enynes influenced by other functional groups such as alcohols, aldehydes, ethers, alkenes or alkynes thus enhancing the molecular complexity of the synthesized products.

Generally,1,n-enynes participated in intramolecular and intermolecular annulation reactions. If the enyne participated in annulation with the functional group present in the same substrate is called intramolecular enyne annulation. If the enyne reacted with other reactants having functional groups such as alkenes, alkynes,

amines, alcohols and carbonyl compounds to give cyclized products is known as intermolecular enyne annulations. 1,n Enyne annulation reactions, enyne-assisted construction of few heterocycles and enyne cyclisation as the key reaction in their total synthesis are also discussed in this section.

SECTION B: "A thioannulation approach to substituted thiophenes from MBH acetates of acetylenic aldehydes"

Thiophenes are significant scaffolds in several biologically active natural products as well as pharmaceuticals. Due to their structural rigidity and distinct electronic properties thiophene derivatives also serve in organic material science. Their potential in chemistry and biology has consistently inspired the pursuit for new methods for thiophene synthesis. The majority of the methods in the literature involves the substitution of thiophene ring *via* metalation or halogenations and suffer from harsh reaction conditions, while thiophene syntheses from the corresponding acyclic precursors are limited, which prompted us to develop a novel thioannulation approach. In this chapter, we reported a novel thioannulation of Morita-Baylis-Hillman acetates of acetylenic aldehydes with KSAc under mild and metal-free reaction conditions. This approach offers a significant advantage over the known thioannulation methods.

During our recent studies, we envisioned that an intermolecular allylic substitution of MBH-acetate of acetylenic aldehyde with a suitable thio-reagent and subsequent deacetylative intramolecular 5-exo-*dig*-thiocycloisomerization in one-pot (two C-S bond formations) would be a convenient process for the synthesis of substituted thiophenes (**Figure 1.1**).

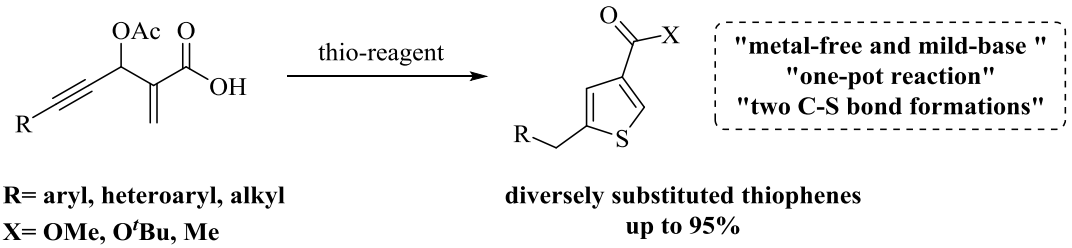
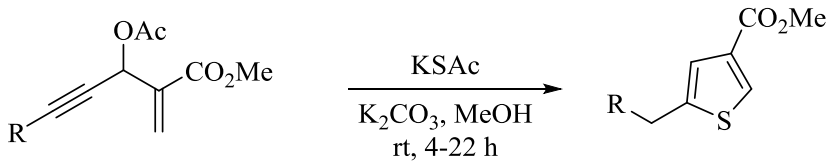


Figure 1.1: [4+1]-Thioannulation of MBH acetates of acetylenic aldehydes

To find the suitable reaction condition for the proposed thioannulation, MBH-acetate **1**, derived from the reaction of 3-phenylpropiolaldehyde with methyl acrylate, was taken as a model substrate. From the optimization studies, it was found that the reaction of **1** with KSAc in the presence of K_2CO_3 produced the thiophene **2** in 94% yield.

Under the optimized conditions, the scope of this annulation reaction using a variety of MBH-acetates of acetylenic aldehydes was investigated and results are summarised in **Table 1.1**. The results revealed that the approach serves as a general and efficient method for the synthesis of diversely substituted thiophenes in good yields.

Table 1.1: Synthesis of 2,4-disubstituted thiophenes[a]

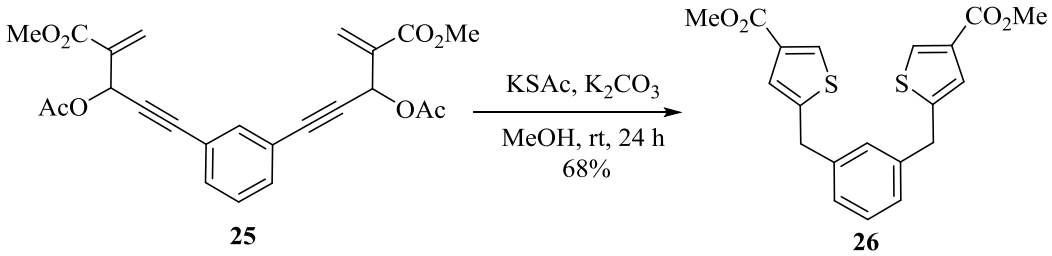


Entry	MBH-Acetate	Time (h)	Thiophene[b]	Yield (%)[c]
1	R = Ph, **1**	18	R = Ph, **2**	94
2	R = *4-Me*-C_6H_4, **3**	20	R = *4-Me*-C_6H_4, **4**	95
3	R = 1-Naphthyl, **5**	22	R =1-Naphthyl, **6**	84
4	R = 4-*MeO*-C_6H_4, **7**	8	R = 4-*MeO*-C_6H_4, **8**	82
5	R = 4-*Cl*-C_6H_4, **9**	6	R = 4-*Cl*-C_6H_4, **10**	73
6	R = *2-I*-C_6H_4, **11**	12	R = *2-I*-C_6H_4, **12**	82
7	R = 3-CF_3-C_6H_4, **13**	8	R = 3-CF_3-C_6H_4, **14**	76
8	R = 3-*NBoc*-Indole, **15**	12	R = 3-*NBoc*-Indole, **16**	69
9	R = 2-Thiophenyl, **17**	8	R = 2-Thiophenyl, **18**	90
10	R = *n*-C_3H_7, **19**	4	R = *n*-C_3H_7, **20**	68
11	R = *n*-C_6H_{13}, **21**	6	R = *n*-C_6H_{13}, **22**	70
12	R = *n*-C_8H_{17}, **23**	4	R = *n*-C_8H_{17}, **24**	62

[a]*Reaction conditions:* MBH-acetate **1** (1 mmol), KSAc (1.1 mmol), K_2CO_3 (2.2 mmol), MeOH (5 mL), rt; [b]All the products were characterized by ^1H, ^{13}C NMR, IR and MS spectra; [c]Isolated yield.

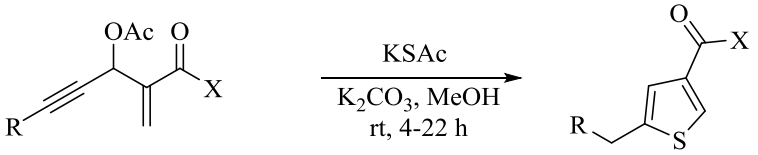
Interestingly, thioannulation of substrate **25** which containing two MBH acetate groups tethered to phenyl ring, with KSAc in the presence of K_2CO_3 in MeOH resulted in a smooth reaction to deliver bis-thiophene **26** in 68% yield (**Scheme 1.1**).

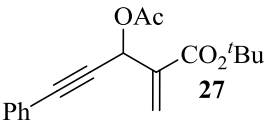
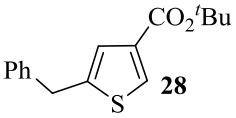
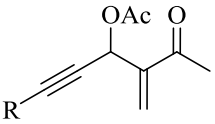
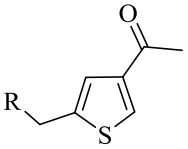
Scheme 1.1: Synthesis of bis-thiophene derivative



We next evaluated the reactivity of diversely substituted MBH-acetates derived from different activated olefins and the results are summarized in **Table 1.2**.

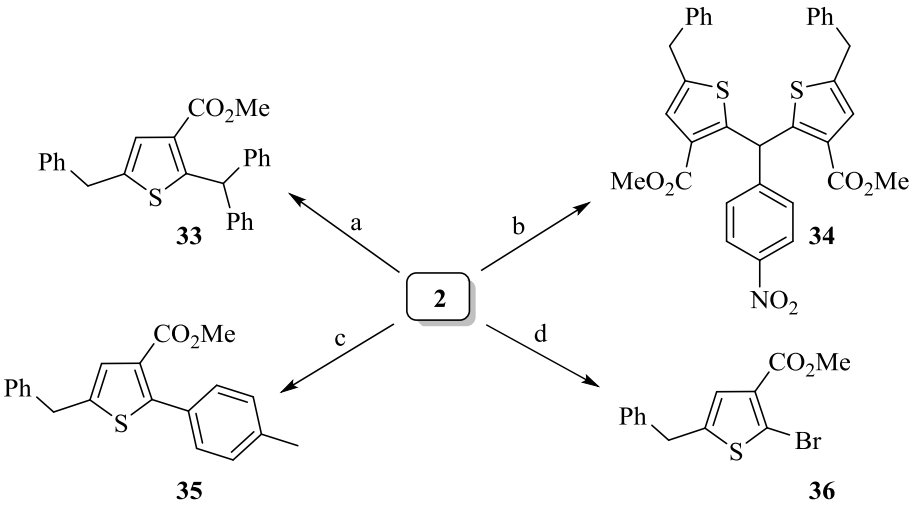
Table 1.2: Thioannulation of MBH-acetates of acetylenic aldehydes with KSAc



Entry	MBH-Acetate	Time (h)	Thiophene	Yield (%)
1	 **27**	6	 **28**	88
2				
	R = Ph, **29**	15	R = Ph, **30**	86
3	R = 4-*MeO*-C_6H_4, **31**	30	R = 4-*MeO*-C_6H_4, **32**	85

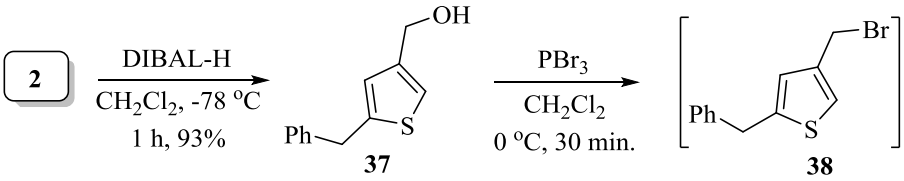
Inspired by these results, we expected that the present reaction could find potential applications in organic synthesis because the obtained thiophenes have two reactive sites: i) C-5 position and ii) C-4 ester group, as a handle for additional diversification. Indeed, this assumption was proved by further investigation using **2** as a substrate (**Scheme 1.2**).

Scheme 1.2: C5-Functionalization reactions of **2**



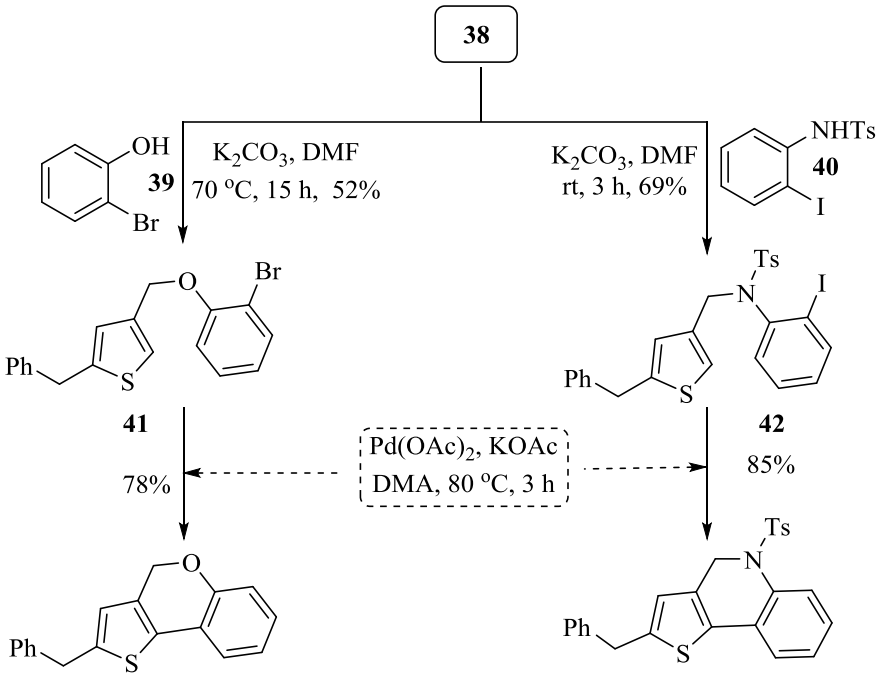
***Reagents and conditions*:** (a) Diphenyl methanol, $BF_3.Et_2O$ (5 mol%), CH_2Cl_2, rt, 1 h, 95%; (b) 4-nitro benzaldehyde, $BF_3.Et_2O$ (20 mol%), CH_2Cl_2, reflux, 24 h, 79%; (c) 4-iodo toluene, $Pd(OAc)_2$ (10 mol%), DMA, 80 ^oC, 12 h, 65%; (d) NBS, CH_3CN, 0 ^oC-rt, 24 h, 81%.

Additionally, thiophene **2** was conveniently utilized in the synthesis of 4*H*-thieno [3, 2-c] chromene (**43**) and thieno [3, 2-c] dihydroquinoline (**44**) as shown in **Scheme 1.3**. Firstly, the ester group of **2** was reduced using DIBAL-H to alcohol **37**, which upon treatment with PBr_3 in CH_2Cl_2 provided the corresponding bromide **38** (**Scheme 1.3**). The bromide **38** was used in *O*-alkylation of 2-bromophenol (**39**) to get **41** and subsequent cyclization through an intramolecular Pd-catalyzed C-H activation offered the desired 4*H*-thieno [3, 2-c] chromene (**43**) in 78% yield. Similarly, *N*-alkylation of 2-iodo *N*-tosylaniline (**40**) with **38** to **42** followed by cyclization gave thieno [3, 2-c] dihydroquinoline (**44**) in good yield (85%).



Scheme 1.3

Scheme 1.3: Synthesis of 4*H*-thieno[3,2-c]chromene (**43**) and thieno[3,2-c]dihydroquinoline (**44**)



4*H*-Thieno[*3,2-c*]chromene, 43 **4,5-Dihydrothieno[*3,2-c*]quinoline, 44**

In conclusion, we have developed a new, versatile and metal-free method for the synthesis of substituted thiophenes from MBH-acetates of acetylenic aldehydes. A simple base (K_2CO_3) promoted the [4+1]-thioannulation of KSAc with MBH-acetates through a tandem allylic substitution followed by deacetylative thiocyclo isomerization (two C-S bond formations).

CHAPTER-II: A novel [4+2]-benzannulation of 3-alkenyl thiophenes/pyrroles with propargylic alcohols to access substituted benzothiophenes/indoles

Indoles and benzothiophenes are an important class of structural frameworks among the benzo-fused heteroaromatic compounds due to their presence in various bioactive natural products and diverse range of pharmaceutically related small molecules. Both have found applications in agrochemicals, optoelectronic materials and pigments. Given this diverse utility, it is highly desirable to develop novel method for the synthesis of these heterocycles. Most of the reported protocols are through the construction of five-membered heterocyclic ring on a pre-functionalized benzene ring. Apart from this, construction of benzene ring on a suitably substituted pyrrole or thiophene are less in number. Herein, we have developed a novel (4+2) benzannulation approach to substituted indoles and benzo thiophenes with 1-aryl/heteroaryl propargylic alcohols in one pot involving sequential propargylation followed by DBU mediated cycloisomerization.

Our interest on the development of novel [4+2]-benzannulations and the utilization of 1-aryl propargylic alcohols as handy synthons towards the synthesis of polycyclic aromatic and heteroaromatic compounds inspired us to explore the present strategy. Accordingly, we envisaged that 2-propargylated 3-alkenyl pyrroles/2-propargylated 3-alkenyl thiophenes would undergo cycloisomerization to give the corresponding Indoles/Benzo thiophenes (**Fig 2.1**).

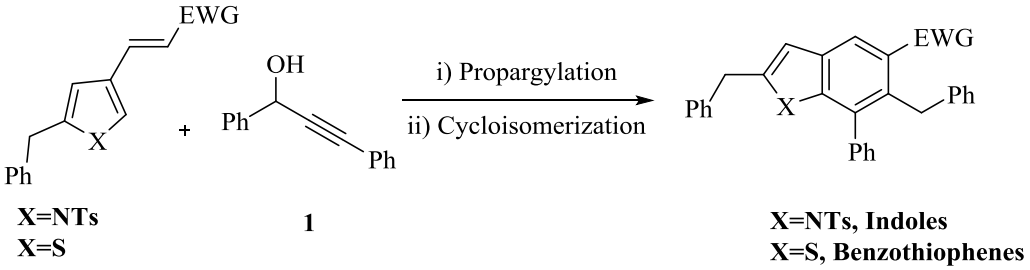
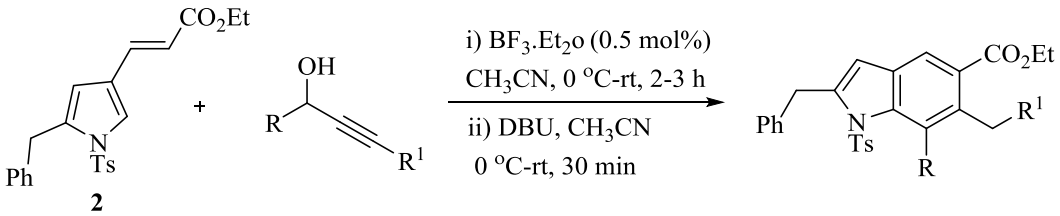


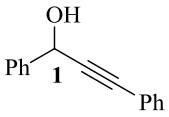
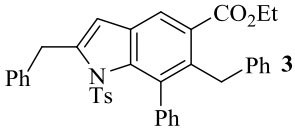
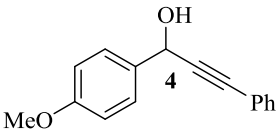
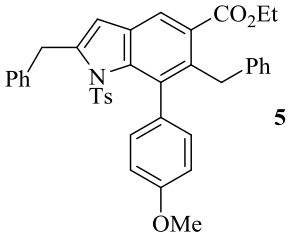
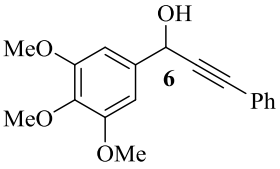
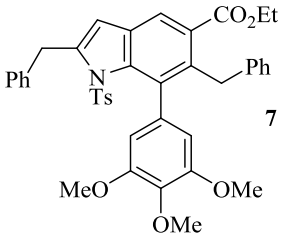
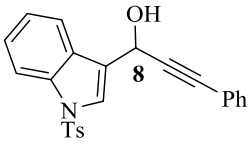
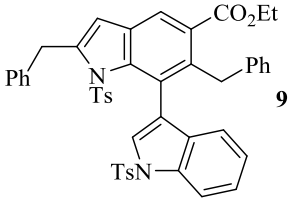
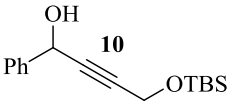
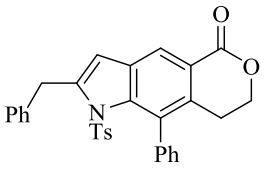
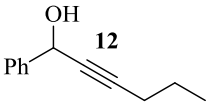
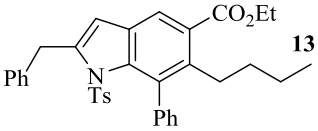
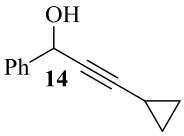
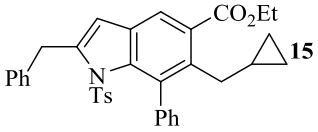
Figure 2.1: [4+2]- Benzannulation reaction of 3-alkenyl pyrrole/3-alkenyl thiophene

To test the hypothesis, alkenyl pyrrole **2** and 1,3-diphenylprop-2-yn-1-ol **1** were chosen as model substrates. From the optimization studies, we were happy to found that the formation of [4+2]-benzannulation product, indole **3** in 90% yield using 5 mol% of $BF_3{\cdot}Et_2O$ in acetonitrile and DBU reaction conditions.

Encouraged by the above result, we examined the substrate scope of this reaction using 3-alkenyl pyrrole **2** with variety of 1-aryl and hereroaryl propargylic alcohols to obtain indoles having diverse substituents and results are summarised in **Table 2.1**. Interestingly the reaction of 3-alkenyl pyrrole **2** with alcohol **10** underwent the desilylative six-membered lactonization during the [4+2]-benzannulation to give dihydropyrano[*3*,*4-f*]indol-5(1*H*)-one **11** in 79% yield (**entry 5, Table 2.1**).

Table 2.1: Scope of propargylic alcohols in [4+2]-benzannulation with **2**

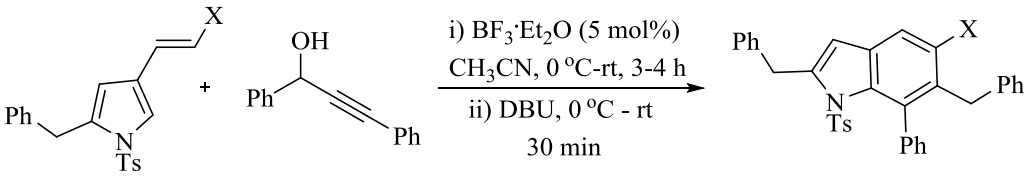


Entry	Propargyl alcohol	time (h)	Indole[a]	yield[b] %
1	 **1**	**3.0/0.5**	 **3**	88
2	 **4**	**3.0/0.5**	 **5**	87
3	 **6**	**2.0/0.5**	 **7**	88
4	 **8**	**2.5/0.5**	 **9**	86
5	 **10**	**2.5/0.5**	 **11**	79
6	 **12**	**2.5/0.5**	 **13**	85
7	 **14**	**3.0/0.5**	 **15**	89

[a]Reaction conditions: $BF_3{\cdot}Et_2O$ (5 mol%), CH_3CN, rt, then DBU rt; [b]Isolated yield

Next the reactivity of diversely substituted 3-alkenylpyrroles having different electron-withdrawing groups with 1,3-diphenylprop-2-yn-1-ol **1** under optimized conditions was evaluated and the results are summarized in **Scheme 2.1**.

Scheme 2.1: Benzannulation of 3-alkenylpyrroes with **1**



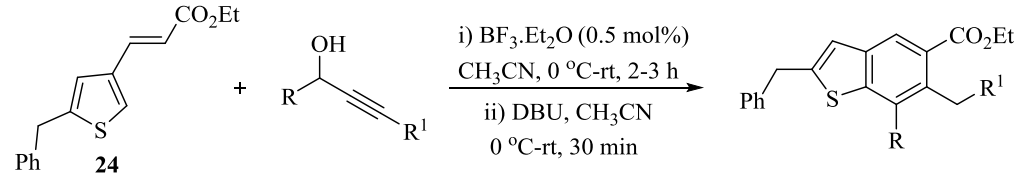
X= COMe, **16**
X= COPh, **18**
X= CN, **20**
X= Ph, **22**

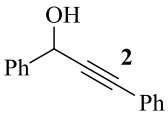
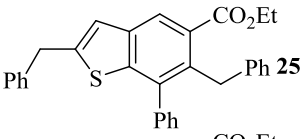
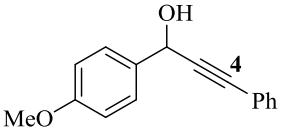
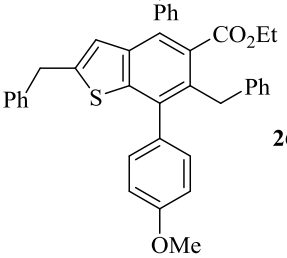
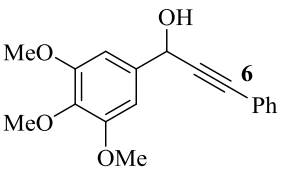
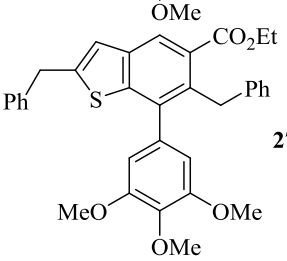
1

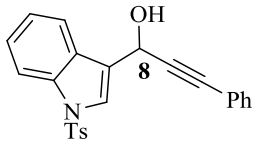
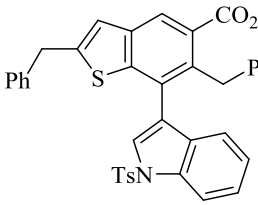
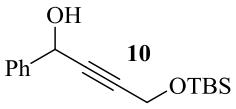
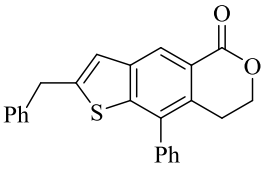
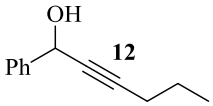
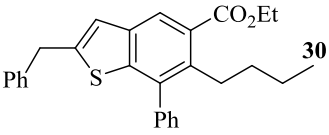
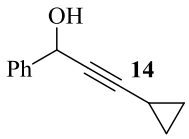
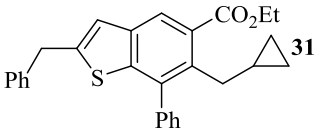
X= COMe, **17**, 87%
X= COPh, **19**, 85%
X= CN, **21**, 89%
X= Ph, **23**, 78%

Further, we extended the present [4+2]-benzannulation reaction for the synthesis of substituted benzothiophenes from the suitably substituted 3-alkenyl thiophene **24** with various 1-aryl/heteroaryl propargylic alcohols under the optimized reaction conditions to obtain a wide variety of substituted benzothiophenes, as shown in **Table 2.2**.

Table 2.2: Scope of propargylic alcohols in [4+2]-benzannulation with **24**

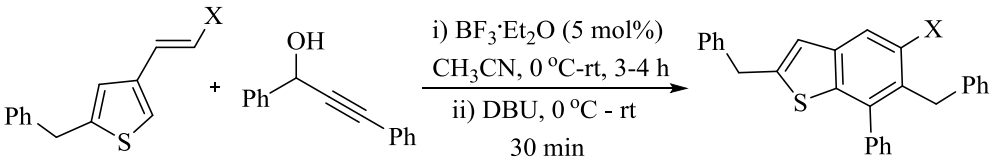


Entry	Propargyl alcohol	time (h)	Benzothiophene	yield %
1	 **2**	3.0/0.5	 **25**	87
2	 **4**	3.0/0.5	 **26**	88
3	 **6**	2.5/0.5	 **27**	88

4		3.0/0.5		**28**	87
5		3.0/0.5		**29**	80
6		2.5/0.5		**30**	86
7		2.5/0.5		**31**	89

We also examined the scope of this [4+2]-benzannulation with a diverse array of 2-alkenyl thiophenes as the diene units and 1,3-diphenylprop-2-yn-1-ol **1** as the two-carbon partner under optimized conditions (**Scheme 2.2**).

Scheme 2.2: [4+2]-Benzannulation of 3-alkenyl thiophenes with **1**



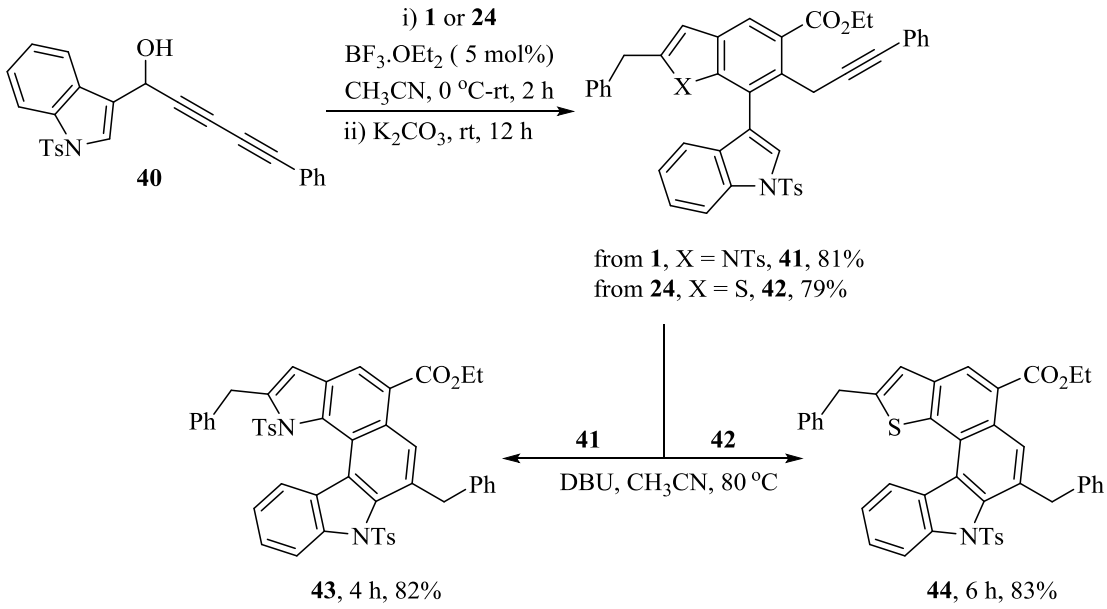
X= COMe, **32**
X= COPh, **34**
X= CN, **36**
X= Ph, **38**

2

X= COMe, **33**, 88%
X= COPh, **35**, 84%
X= CN, **37**, 89%
X= Ph, **39**, 80%

Encouraged by the results, we tried to apply the benzannulation of 2-alkenylpyrrole **2** with a diynyl alcohol, 5-phenyl-1-(1-tosyl-1H-indol-3-yl)penta-2,4-diyn-1-ol (**40**) towards the double cyclization product successfully and observed the formation of diaza[5]helicene **43** (82%) *via* the mono-cyclized indole **41** (81%, **Scheme 3.3**). Similarly, the reaction of 2-alkenylbenzothiophene **24** with 2,4-diyn-1-ol **40** underwent the sequential propargylation followed by double cycloisomerization (dibenzannulation) to yield **44** (83%) *via* benzothiophene **42** (79%. **Scheme 2.3**).

Scheme 2.3: Synthesis of aza[5]helicenes through dibenzannulation



In summary, we have developed an efficient method for the synthesis of multisubstituted indoles/benzo thiophenes *via* the [4+2] benzannulation of 3-alkenyl pyrrole/3-alkenyl thiophene with 1-aryl propargylic alcohols. This method has several advantages such as mild and metal-free reaction conditions, wide substrate scope from readily accessible starting materials. In addition, an efficient dibenzannulation of 2,4-diyn-1-ol was also recognized, thus providing a facile access to aza[5]helicenes.

CHAPTER III: One-pot sequential Propargylation/Cycloisomerization strategy to diversely substituted carbazoles and aryl or heteroaryl annulated[*a*]carbazoles

The carbazole scaffold represents an important structural constituent in numerous natural products and synthetic compounds showing a wide variety of biological and pharmaceutical activities. In addition, they also useful as photorefractive materials as well as organic dyes for solar cells. Thus, the synthesis of carbazole derivatives has attracted much attention and various strategies have been developed. Among these, benzannulation of indoles has received substantial attention to construct the substituted carbazoles due to the easy accessibility of indole substances. In particular, the alkyne/allene-assisted formation of benzene ring on indole moiety is attractive. Herein, we report a novel [4+2]-benzannulation of 2-alkenyl/aryl indoles with 1-aryl propargylic alcohols. This method offers a substantial

advantage by providing an access to diverse carbazoles as well as aryl or heteroaryl-annulated[*a*]carbazoles from readily accessible substrates.

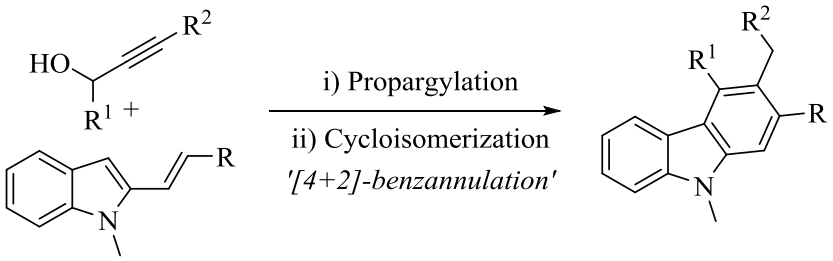
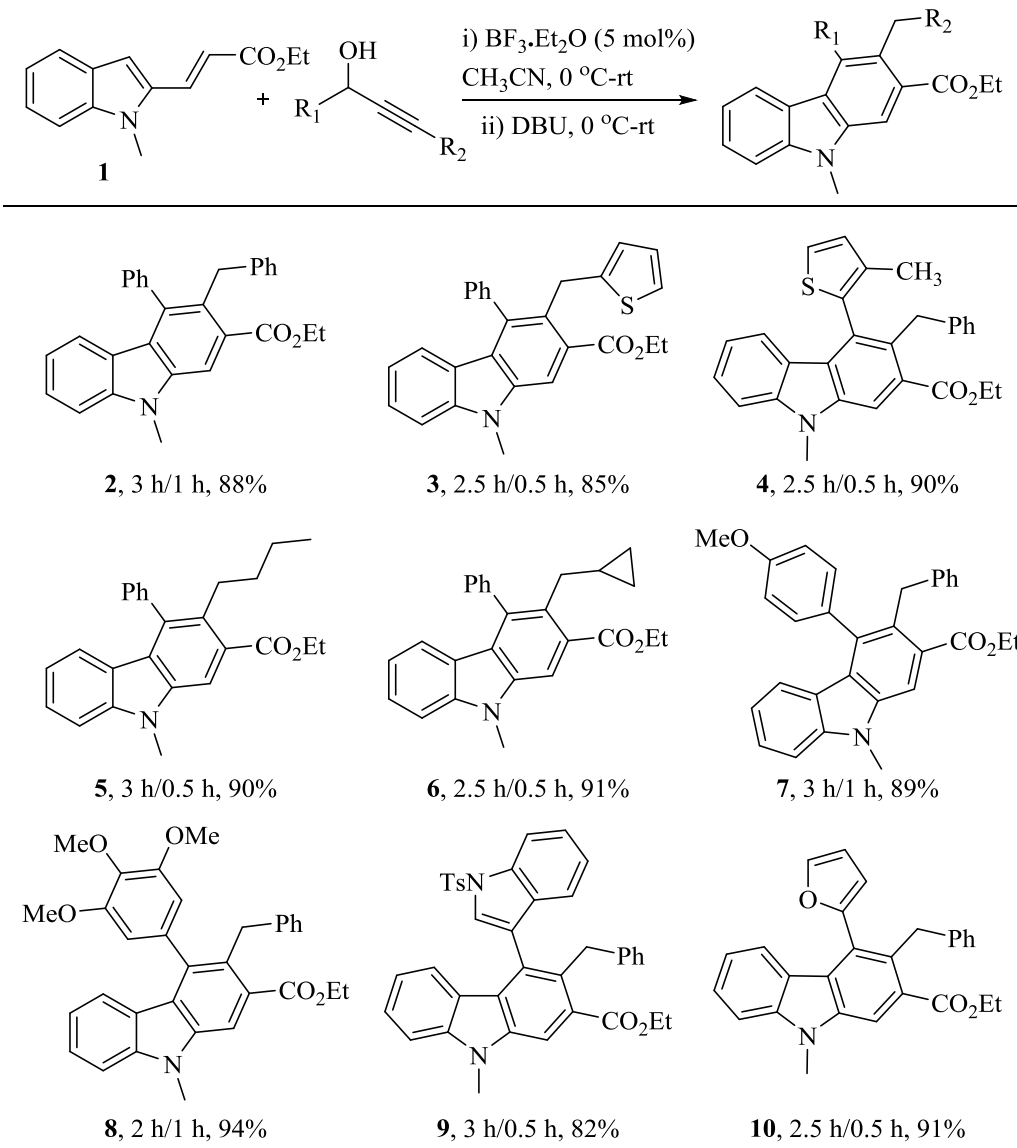


Figure 3.1: Intermolecular annulation of alkenyl indoles with propargylic alcohols

Based on our studies on enyne-based annulation reactions and use of 1-aryl propargylic alcohols as useful synthon, we envisioned that 3-propargylated 2-alkenyl indoles would undergo cycloisomerization to give the corresponding carbazoles (**Figure 3.1**). For testing this hypothesis, the 2-alkenyl indole **1** and 1, 3-diphenylprop-2-yn-1-ol **11** were chosen as starting materials. The propargylation of alkenyl indole **1** was verified in the presence of few acid-catalysts such as $BF_3{\cdot}Et_2O$ (5 mol%), $FeCl_3$, *p*TSA, I_2 and $AlCl_3$. Next, the cycloisomerization was tested using different bases and found that 5 mol% $BF_3{\cdot}Et_2O$ followed by DBU in CH_3CN was the suitable condition for one-pot synthesis of carbazole **2**. Encouraged by this result, a range of diversely substituted propargylic alcohols was investigated with **1** as a typical reaction partner. All propargylic alcohols (bearing aryl, heteroaryl, alkyl and cyclopropyl groups on the alkyne), and having aryl, substituted aryl, heteroaryl groups at the C1-position) gave the corresponding carbazoles in good yields (**Scheme 3.1**).

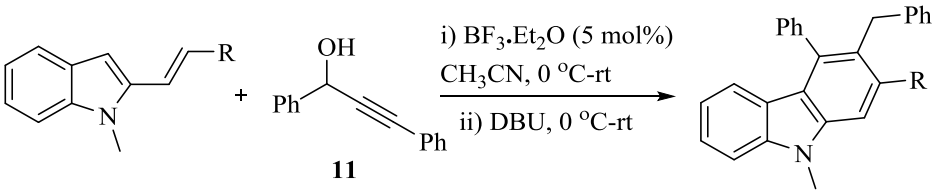
Scheme 3.1: Scope of propargylic alcohols in [4+2]-benzannulation with **1**

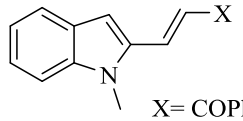
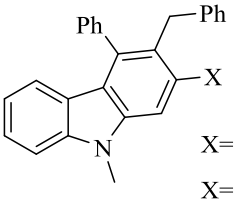
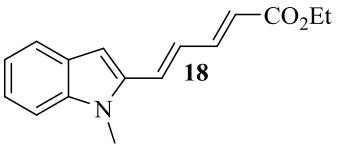
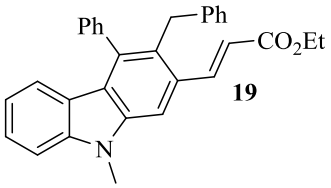
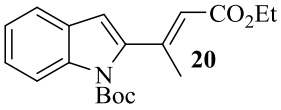
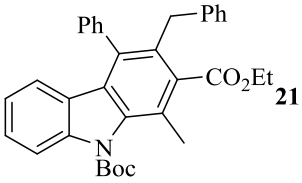
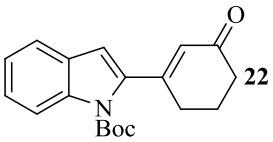
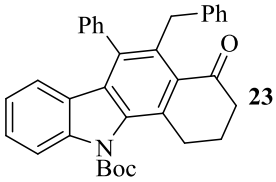
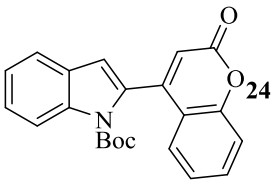
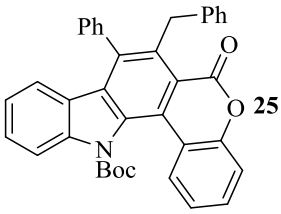
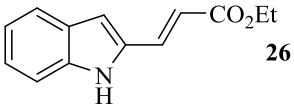
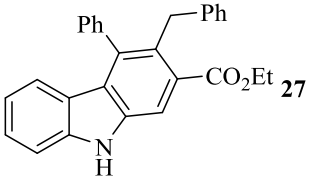


Reaction conditions: **1** (1 equiv), propargylic alcohol (1.1 equiv), i) $BF_3.Et_2O$ (5 mol %), CH_3CN (10 mL/mmol), rt ii) DBU (1 equiv)

The scope of this [4+2]-benzannulation was also examined with a diverse array of 2-alkenyl indoles as the diene units and 1,3-diphenylprop-2-yn-1-ol **11** as the two-carbon partner under optimized conditions as shown in **Table 3.1**.

Table 3. 1: [4+2]-Benzannulation of 2-alkenyl indoles with **11**



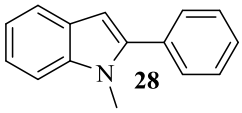
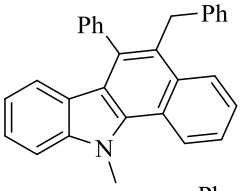
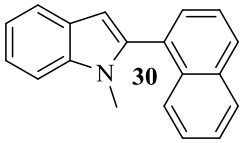
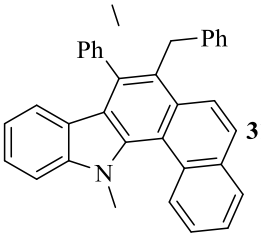
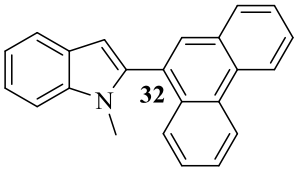
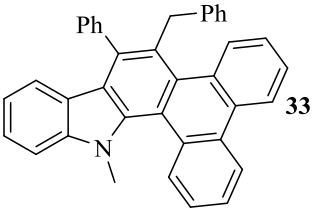
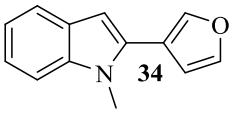
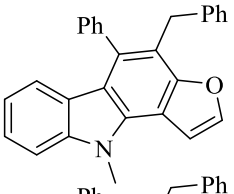
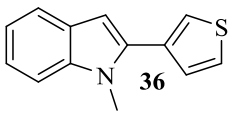
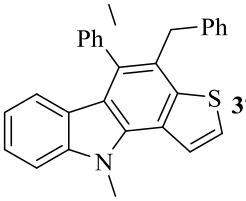
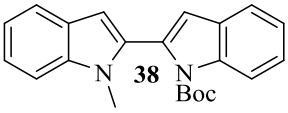
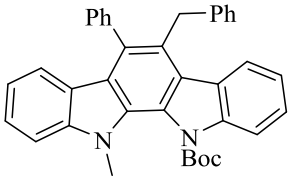
entry	2-alkenyl indole	reaction time (h)	Carbazole	yield (%)[a]
1				
	X= COPh, **12**	3.5/1	X= COPh, **13**	84
	X= COMe, **14**	4/1	X= COMe, **15**	82
	X= CN, **16**	3/0.5	X= CN, **17**	90
2	 **18**	3.5/0.5	 **19**	80
3	 **20**	3/1	 **21**	81
4	 **22**	2.5/0.5	 **23**	83
5	 **24**	2.5/0.5	 **25**	74
6[b]	 **26**	3/0.5	 **27**	92

Reaction conditions: alkenyl indole (1 equiv), propargylic alcohol (1.1 equiv) i) $BF_3.Et_2O$ (5 mol %), CH_3CN (10 mL/mmol), rt ii) DBU (1 equiv), [a]Isolated yield, [b]K_2CO_3 used.

The above-mentioned successful results encouraged us to extend the present method for the synthesis of aryl and hetero aryl-annulated[*a*]carabazoles as presented

in **Table 3.2**, core of several bioactive natural products, were also synthesized with the present protocol from the respective 2-aryl/heteroaryl indoles.

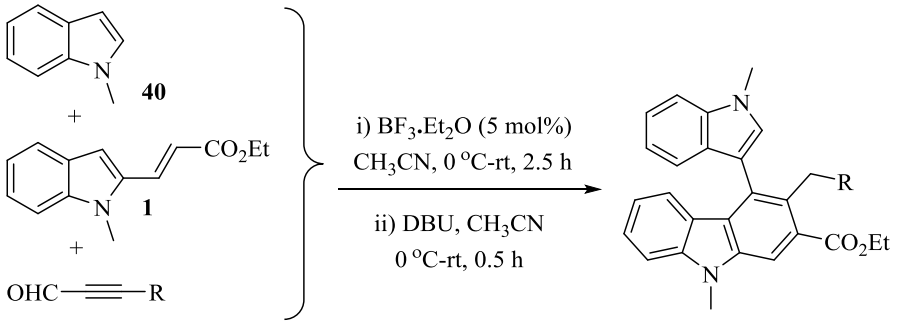
Table 3.2: [4+2]-Benzannulation of 2-aryl/heteroaryl indoles with **2**

entry	2-aryl/heteroaryl indole	reaction time step i/ii (h)	Carbazole	yield (%)[b]
1	 **28**	2/11	 **29**	65
2	 **30**	2/9	 **31**	74
3	 **32**	2/10	 **33**	72
4	 **34**	1/4	 **35**	81
5	 **36**	1/5	 **37**	80
6	 **38** Boc	1.5/4	 **39**	58

[a]Reaction conditions: aryl/heteroaryl indole (1 equiv), **2** (1.1 equiv), i). $BF_3.Et_2O$ (5 mol %), CH_3CN (10 mL/mmol), rt, ii) DBU (1 equiv), reflux; [b]Isolated yield

Interestingly, we have developed a three-component coupling reaction with the help of alkenyl indole, propargylic aldehyde and *N*-Methyl indole under $BF_3{\cdot}Et_2O$/DBU in CH_3CN conditions to provide 5-indoloyl carbazoles (**Scheme 3.2**) in good yields.

Scheme 3.2: Three-component approach to 5-indoloyl carbazoles

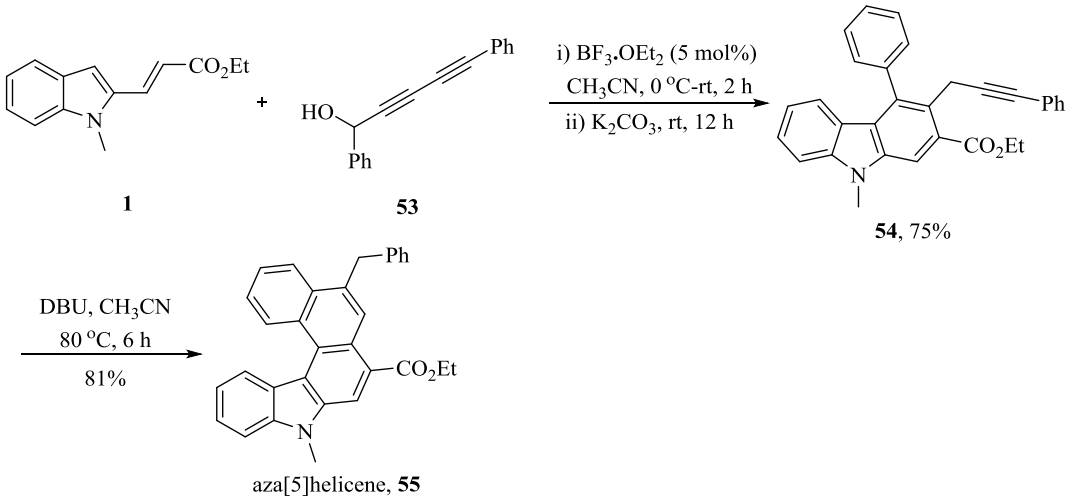


R = Ph, **41**
R = 4-Me-Ph, **43**
R = 4-MeO-Ph, **45**
R = 3-CF_3-Ph, **47**
R = 4-Cl-Ph, **49**
R = 2-Thiophenyl, **51**

R = Ph, **42**, 82%
R = 4-Me-Ph, **44**, 81%
R = 4-MeO-Ph, **46**, 82%
R = 3-CF_3-Ph, **48**, 78%
R = 4-Cl-Ph, **50**, 82%
R = 2-Thiophenyl, **52**, 83%

The application of the present protocol was explored for the construction of carbazole-based azahelicene, valuable motifs in various applications. The use of 1,5-diphenylpenta-2,4-diyn-1-ol (**53**) in reaction with **1** facilitated the double cyclization to give the aza [5]helicene **61** *via* the monocyclized intermediate **60** (**Scheme 3.3**).

Scheme 3.3: Synthesis of aza [5] helicene **55**



In summary, an effective method for the synthesis of multisubstituted carbazoles *via* the [4+2] benzannulation of 2-alkenyl/aryl/heteroaryl indoles with 1-aryl propargylic alcohols has been developed. This method offers several advantages such as mild and metal-free reaction conditions, wide substrate scope from easily accessible starting materials. A library of structurally varied carbazoles, in particular aryl or heteroaryl-annulated[*a*]carabazoles should be easily accessible. An interesting three-component reaction to indole-substituted carbazoles was established. The method was also gave a new entry to aza[5]helicene.